



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Au-Catalyzed Biaryl Coupling To Generate 5- to 9-Membered Rings: Turnover-Limiting Reductive Elimination versus -Complexation

Citation for published version:

Corrie, TJA, Ball, LT, Russell, CA & Lloyd-jones, GC 2017, 'Au-Catalyzed Biaryl Coupling To Generate 5- to 9-Membered Rings: Turnover-Limiting Reductive Elimination versus -Complexation', *Journal of the American Chemical Society*, vol. 139, no. 1, pp. 245-254. <https://doi.org/10.1021/jacs.6b10018>

Digital Object Identifier (DOI):

[10.1021/jacs.6b10018](https://doi.org/10.1021/jacs.6b10018)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of the American Chemical Society

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Au-catalyzed Biaryl Coupling to Generate 5- to 9-membered Rings: Turnover-Limiting Reductive Elimination versus π -complexation

Tom J. A. Corrie,[†] Liam T. Ball,^{†,§} Christopher A. Russell,[§] and Guy C. Lloyd-Jones^{*,†}

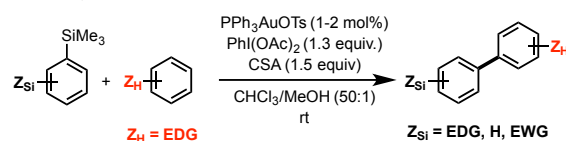
[†]University of Edinburgh, EaStChem, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, U.K.

[§]School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K.

ABSTRACT: The intramolecular gold-catalyzed arylation of arenes by aryltrimethylsilanes has been investigated from both a mechanistic and preparative aspect. The reaction generates five to nine membered rings, and of the 44 examples studied, ten include a heteroatom (*N*, *O*). The tethering of the arene to the arylsilane not only provides a tool to probe the impact of the conformational flexibility of Ar–Au–Ar intermediates, via systematic modulation of the length of aryl-aryl linkage, but also the ability to arylate neutral and electron-poor arenes - substrates that do not react at all in the intermolecular process. Rendering the arylation intramolecular also results in phenomenologically simpler reaction kinetics, and overall these features have facilitated a detailed study of linear free energy relationships, kinetic isotope effects, and the first quantitative experimental data on the effects of aryl electron-demand and conformational freedom on the rate of reductive elimination from diaryl gold(III) species. The turnover-limiting step for the formation of a series of fluorene derivatives is sensitive to the reactivity of the arene and changes from reductive elimination to π -complexation for arenes bearing strongly electron-withdrawing substituents ($\sigma > 0.43$). Reductive elimination is accelerated by electron-donating substituents ($\rho = -2.0$) on one or both rings, with the individual σ -values being additive in nature. Longer and more flexible tethers between the two aryl rings results in faster reductive elimination from Ar–Au(X)–Ar, and to the π -complexation of the arene by Ar–AuX₂ becoming the turnover-limiting step.

Introduction

Transition metal-catalyzed cross-coupling has revolutionized synthesis,¹ with the biaryl motif a major focal point for research in this area.² The union of aryl-(pseudo)halides and aryl-metallic reagents have been extensively studied, and there is now substantial interest in more step- and atom-economic variants. In this regard, the reaction of arenes with aryl-metallic reagents, one class of the so-called 'direct arylation' reaction, has received significant attention.³ Catalysis by gold is emerging as a powerful synthetic tool.⁴ We recently reported a gold-catalyzed *intermolecular* arylation of electron-rich arenes by aryltrimethylsilanes (Scheme 1).⁵



Scheme 1. Au-catalyzed intermolecular arene-arylsilane oxidative coupling, as initially reported (2012).⁵ CSA = camphorsulfonic acid. For further advances, see references 6-8.

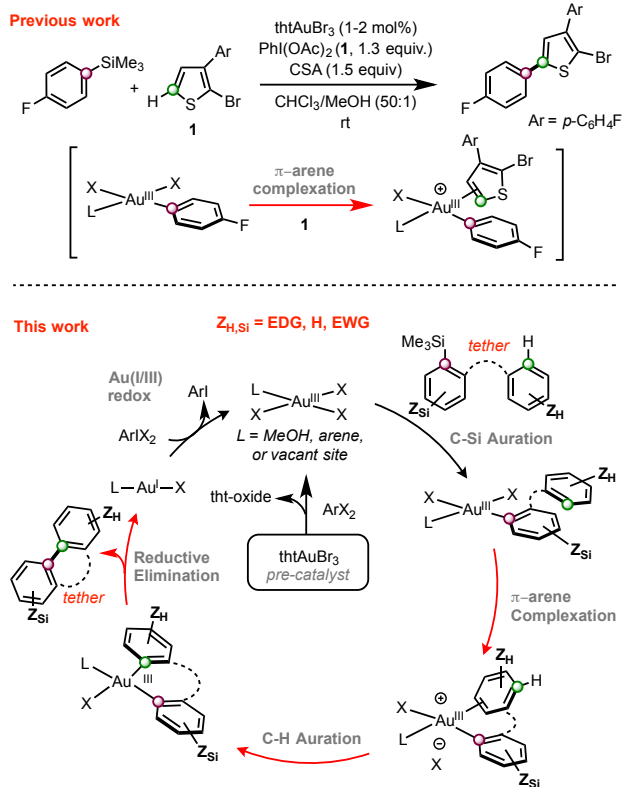
The process is operationally simple, proceeds under air, often at room temperature, at low catalyst loadings (1-2 mol%), and with broad functional-group tolerance. In subsequent developments, Itami and Sagawa demonstrated that pyridylidene Au-complexation facilitates arylation of isoxazoles, indoles and benzothiophenes,⁶ Jeon applied Au-catalyzed arylation to functionalize *ortho*-silyl aryl triflates generated via Rh/Ir-catalyzed traceless *ortho*-CH silylation,⁷ and we reported that silane and

oxidant modification allows arylation of a range of heterocycles.⁸

Major advances have also been made towards understanding the unique reactivity and selectivity of catalytic reactions proceeding via Au(I) and Au(III) intermediates.^{6,9} Nonetheless, in comparison to many transition metal catalyzed processes, mechanistic understanding of homogeneous gold catalysis remains less well developed. In 2014 we reported our initial mechanistic investigations into the gold-catalyzed *intermolecular* arylation (Scheme 1).^{9h} Study of the pre-catalyst activation process revealed that during an approximately 2 hour-long induction period, the Au(I)-phosphine complex was oxidized to yield PPh₃O and the active gold catalyst: a solvated AuX₃ species (X = CSA, OTs). By changing to a tHtAuBr₃ pre-catalyst (tHt = tetrahydrothiophene) we were able to reduce the induction period to around 300 seconds; again liberating a solvated 'ligand-free' AuX₃ species. Using this pre-catalyst system and a specifically tailored substrate (arylthiophene 1, Scheme 2, upper) the reaction kinetics were sufficiently tractable to allow us to determine the empirical rate law by ¹⁹F NMR, and to deduce that intermolecular Au(III)-arene π -complexation is the turnover-limiting step.^{9h} However, our conclusions were predominantly based on detailed study of this single well-behaved model system. Information on some of the other steps in the cycle was less clear, being gained indirectly from competition experiments, literature precedent, and model stoichiometric reactions.

Gaining mechanistic insight to other steps in the cycle has become an important goal. However, to date the process has been limited to π -rich arenes and some heterocycles. Neutral or

electron-poor arenes act solely as spectators to the competing homocoupling of the aryl trimethylsilane. This substantially limits the range of arenes that can be explored in, for example, linear free-energy relationships, even by way of analysis of relative rather than absolute rates.



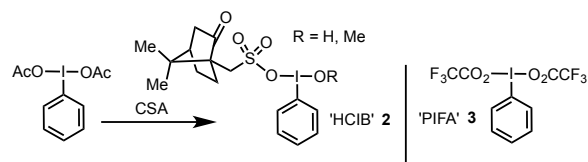
Scheme 2. Mechanistic studies of Au-catalyzed arene-arylsilane oxidative coupling. tht = tetrahydrothiophene. CSA = camphorsulfonic acid. L, X = unspecified neutral and anionic ligands. The intermolecular process^{9h} is limited to π -rich arenes.

Herein we report on the *intramolecular* process (Scheme 2, lower). Conducting the arylation intramolecularly induces a number of useful changes to the system: i) in contrast to the intermolecular reaction, the reactions proceed with very reproducible and, in the main, phenomenologically-simple kinetics, *vide infra*; ii) a very broad range of arenes, including highly electron-deficient examples, can be arylated without competing arylsilane homocoupling; and iii), the tether between the arene and the aryl silane can be used to systematically perturb arene-Au conformational flexibility, and to modulate the effective molarity of arene, in the catalytic intermediates. Overall the intramolecular system allows substitution patterns (Z_{Si} and Z_H) and tether lengths to be tuned to provide the reactivity and kinetic regulation requisite for elucidation of mechanistic features that are *not accessible in the intermolecular version*. Using this platform we have gained insight into arene auration, Wheland intermediate generation and, uniquely, reductive elimination.

Results and Discussion

Preparative Arylation We began by exploring preparative cyclization, using 'HCIB' (2) or 'PIFA', (3) as the oxidant, and the rapidly-activating pre-catalyst thtAuBr_3 (*vide supra*)^{9h} in $\text{CHCl}_3/\text{MeOH}$ at 27 °C. A series of 35 aryl-TMS substrates

(Tables 1 and 2) were cyclized, affording 5- to 9-membered rings in good to excellent isolated yields.



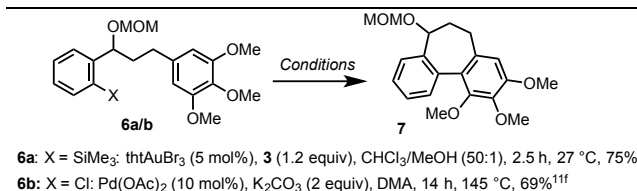
The structures of the largest rings (5ah, 5ai, Table 2, entries 17,18) were confirmed by single crystal X-ray diffraction. Although a number of other intramolecular direct arylation strategies have been reported,¹⁰ the gold-catalyzed cyclization displays excellent functional group tolerance, proceeds at low reaction temperatures, uses readily prepared TMS-bearing starting materials, and yields 5-9 membered ring products bearing a diverse range of substituents, from *m*-CF₃ to *p*-OMe. For the majority of examples, 1-2 mol% Au allowed complete conversion, at 27 °C in a reasonable timescale; with some substrates substantially lower loadings were possible. For example cyclization of 4n (Table 2, entry 3) was complete in under 10 minutes using 1 mol% Au (95% yield) and at 0.06 mol% Au still afforded dimethylfluorene 5n in 80% yield, with formal turnover number of 1330. In contrast, the cyclization of 4ah (Table 2, entry 17) to generate 8-membered 5ah required 4 mol% Au, and 9-membered 5ai (Table 2, entry 18), required heating to 50 °C (52% yield). Although the formation of 8- and 9- membered rings *via* metal catalyzed direct arylation has been reported,¹¹ examples involving simple aryl rings (no directing groups) are rare.

In some cases, in particular anisyl and naphthyl substrates 4a, 4i and 4s, oxidant (HCIB, 2)¹² reacts directly with electron-rich arene to generate a diaryliodonium salt *via* an $\text{S}_{\text{E}}\text{Ar}$ mechanism.¹³ This competing process, which is not Au-catalyzed, severely reduced the yield with certain examples. Changing from HCIB (2) to PIFA (3) largely eliminated diaryliodonium formation, allowing 5a, 5i and 5s to be obtained in 80-88% yields. The impact of oxidant is exemplified in the cyclization of 4a, Table 1.

Table 1. Effect of oxidant (2, 3) on the cyclization of 4a.

thtAuBr ₃	Conversion of 4a to 5a	
	HCIB (2) ^a	PIFA (3) ^b
0.25 mol%	11%	85%
0.5 mol%	17%	90%
1 mol%	33%	88%
2 mol%	42%	90%

^a generated in situ from PhI(OAc)₂ (1.1 equiv) + CSA (1.3 equiv). ^bPIFA (3, 1.1 equiv). Conversion by ¹H NMR using internal standard (CH₂Br₂).

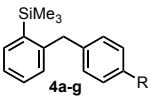
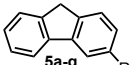
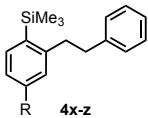
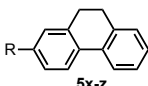
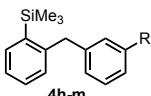
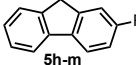
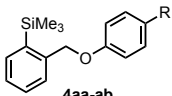
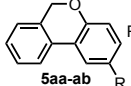
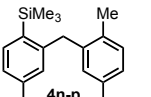
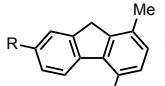
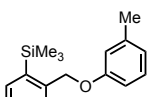
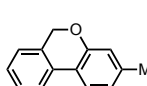
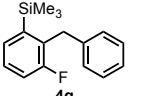
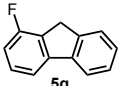
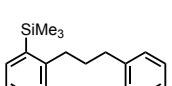
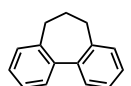
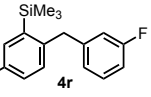
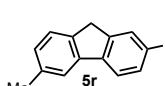
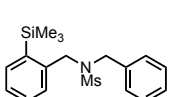
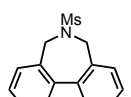
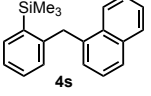
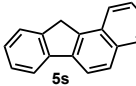
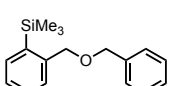
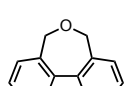
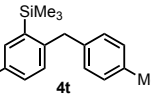
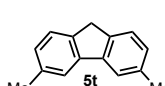
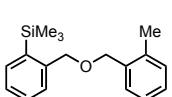
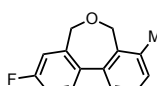
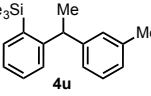
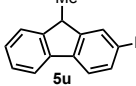
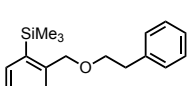
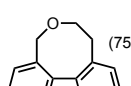
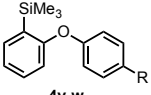
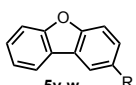
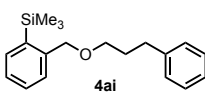
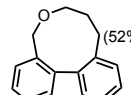


Scheme 3. Au / Pd catalyzed direct arylation of 6a / 6b.

Suppression of the background diaryliodonium formation using PIFA (**3**) allows substantially lower catalyst loadings to be employed.¹⁴ The beneficial effect of replacing HCIB (**2**) with PIFA (**3**) was further explored by conversion of **6a** (X = TMS) to **7**, Scheme 3, requiring arylation of a highly electron-rich trimethoxy benzene ring.¹⁵ Thus, whilst HCIB (**2**) led to a com-

plex mixture, due to diaryliodonium salt generation and acid-mediated *in situ* MOM deprotection, use of PIFA (**3**) afforded the 7-membered ring allocolchinoid skeleton¹⁵ **7** in 75% yield, with the MOM group intact. An analogous Pd-catalyzed process using **6b** (X = Cl) requires substantially more forcing conditions (145 °C).^{11f}

Table 2. Preparative gold-catalyzed cyclizations (35 examples) of **4a-4ai** to **5a-5ai** at 27 °C.^a

Entry	Substrate	Product	(Yield, Time)	Entry	Substrate	Product	(Yield, Time)
1			R = OMe (88%, 2 h) ^b 5a	10			R = H (72%, 1 h) 5x
			H (94%, 1 h) 5b				Cl (91%, 1 h) ^c 5y
			t-Bu (81%, 1 h) 5c				CF ₃ (82%, 16 h) ^c 5z
			Cl (90%, 4 h) 5d				
			OPiv (81%, 6 h) 5e				
			CF ₃ (80%, 15 h) 5f				
			OTf (92%, 16 h) ^c 5g				
2			R = Me (95%, 1 h) ^d 5h	11			R = H (86%, 2 h) ^{c,f} 5aa
			OMe (80%, 1 h) ^{b,d} 5i				t-Bu (60%, 1 h) ^{c,f} 5ab
			F (85%, 2 h) ^d 5j				
			Cl (90%, 3 h) ^d 5k				
			CF ₃ (88%, 16 h) ^{d,e} 5l				
			OTf (78%, 15 h) ^d 5m				
3			R = H (95%, 10 min) 5n	12			(86%, 1 h) ^{e,c,f}
			F (89%, 15 min) 5o				
			Cl (91%, 1 h) ^c 5p				
4			(87%, 16 h)	13			(85%, 15 h) ^c
5			(89%, 5 h)	14			(73%, 16 h) ^c
6			(80%, 1 h) ^b	15			(76%, 16 h) ^{c,e}
7			(76%, 1 h)	16			(82%, 15 h) ^c
8			(79%, 1 h) ^{b,c,d}	17			(75%, 14 h) ^g
9			R = H (87%, 30 min) 5v	18			(52%, 16 h) ^{e,g,h}
			R = CH ₂ NPhth (94%, 1 h) 5w				

^aUnless otherwise stated: **4** (0.50 mmol), tHtAuBr₃ (1 mol%), PhI(OAc)₂ (0.55 mmol), CSA (0.65 mmol) in CHCl₃/MeOH (50:1, 0.1 M). ^bPhI(OCOCF₃)₂ **3**, (0.55 mmol) replaces **1**/CSA. ^ctHtAuBr₃ (2 mol%). ^dRatio of 2-/4-regioisomers: **5h** (95:5), **5i** (88:12), **5j** (97:3), **5u** (97:3) and 3-/1-regioisomers: **5ac** (89:11). ^eCSA (1.0 mmol). ^f0.05 M **4**. ^gtHtAuBr₃ (4 mol%). ^h50 °C. Phth = phthalimido. Piv = t-BuCO₂.

Mechanistic Study The intramolecular arylation, particularly the examples generating substituted fluorene products¹⁶ (entries 1-8, Table 2), proved ideal for mechanistic study. Firstly, as noted above, the intramolecular process tolerates a very much larger range of arene substituents than the intermolecular version, where only electron rich arenes are tolerated. This key feature has allowed detailed analysis of linear free energy relationships - both for the silane and the arene. Secondly, the reactions tend to proceed with reproducible and (phenomenologically) simple kinetics, often pseudo zero-order *vide infra*, without significant side-product formation. In contrast, the intermolecular system display complex kinetic profiles and often suffers from competing aryl silane homocoupling. Thirdly, deuterium labels can be readily installed at strategic positions to analyze for KIEs at key steps. And finally, the tether length between the arenes is readily varied, allowing the kinetics of intramolecular arene capture to be modulated. Overall, in combination with earlier data,^{9h} the system allows a more holistic analysis of the catalytic cycle.

Kinetics and Activation Parameters In our previous investigation of the *intermolecular* reaction (Scheme 2, upper), arene π -complexation was found to be the turnover-limiting step, leading to pseudo first-order kinetics.^{9h} By tethering the arene to the arylsilane, and thus in turn to the aryl-gold, the effective molarity of the arene is raised, potentially leading to the turnover limiting step being driven to another stage in the cycle. Monitoring of the reaction of **4b** by ¹H NMR spectroscopy revealed the expected^{9h} induction period (approx 300 seconds) during which the catalyst is converted to the tht-free active species LAuX₃, where L = MeOH, arene, or vacant site; X = CSA, and up to one Br. After completion of the induction period, catalytic turnover proceeds with clean pseudo-zero order kinetics, turning-over for the full reaction evolution at a formal frequency of 0.07 s⁻¹ at 27 °C (Figure 1, top).

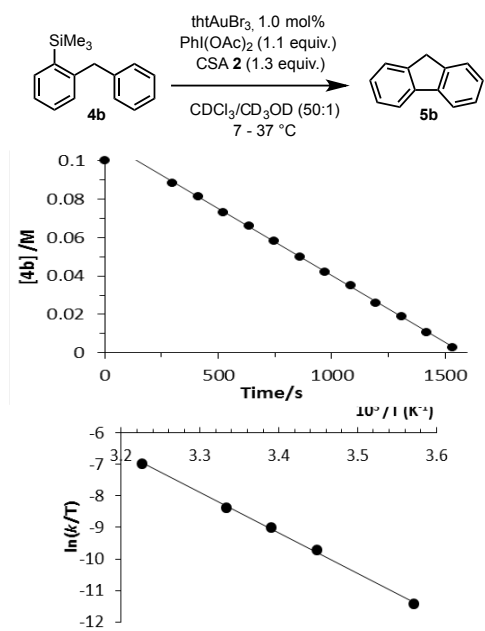
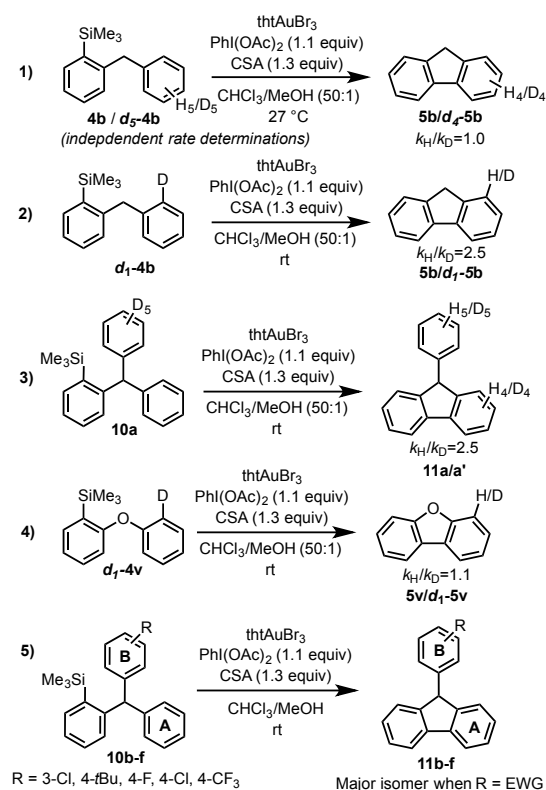


Figure 1. Top: Pseudo-zero order kinetics for consumption of **4b** in Au-catalyzed cyclization at 27 °C; $d[4b]/dt = -k_{\text{obs}}t$; where $k_{\text{obs}} = 7 \times 10^{-5} \text{ Ms}^{-1}$; $R^2 = 0.99$. Bottom: Eyring analysis for cyclization of **4b** (0.1 M) with 1 mol% Au, $\ln(k/T) = 34.54 - (12.86 \times 10^3/T)$; $R^2 = 1.00$; $\Delta H^\ddagger = +26 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = +21 \text{ e.u.}$

The pseudo-zero order kinetics preclude an intermolecular turnover limiting step, or an intermolecular pre-equilibrium, and thus cannot involve Au(I/III) redox by PhIX₂, or C-Si auration (Scheme 2). In a general sense, this confines the turnover-rate limiting step to being one of: intramolecular π -complexation, C-H auration, reductive elimination, ligand dissociation, or intra-complex reorganization / isomerization.

Eyring analysis, between 7 and 37 °C, afforded $\Delta S^\ddagger = +21 \text{ e.u.}$ (Figure 1, lower); opposite in sign to the intermolecular arylation (Scheme 2 upper) where turnover-rate limiting π -complexation induces a strongly negative ΔS^\ddagger .^{9h} Although interpretation of activation parameters must be taken with care, the results suggest that the turnover-rate limiting step for the *intramolecular* system occurs *after* π -complexation, which would be expected to induce a small but negative ΔS^\ddagger . Further experiments were performed to deduce which unimolecular process, prior to bimolecular Au(I/III) redox, is turnover-rate limiting.

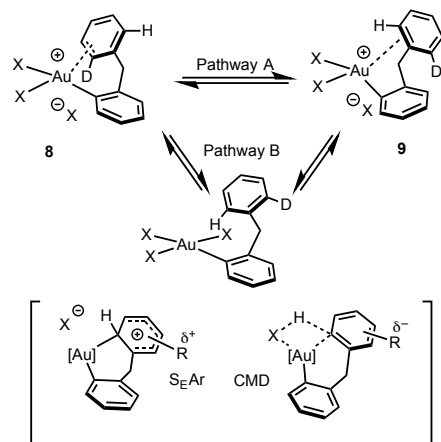
Deuterium Kinetic Isotope Effects In order to probe the C-H auration, a range of deuterated substrates were deployed in intramolecular arylation, Scheme 4, equations 1-4. Control experiments confirmed that there is no deuterium-protium exchange before, during, or after cyclization, indicating that overall C-H / C-D cleavage is irreversible. The absolute rates of turnover of **4b** versus **d₅-4b** (Scheme 4, equation 1) were experimentally indistinguishable ($k_H/k_D = 1.0$). Thus the perdeuterated phenyl ring induces no significant primary or secondary kinetic isotope effect (KIE) on the overall rate of catalytic turnover. This eliminates C-H cleavage from consideration as the turnover-rate limiting step.



Scheme 4. KIEs (1-4) and substituent partitioning (5) for intramolecular Au-catalyzed arylation.

As noted by Schmidbaur, " η^2 -coordination to unsaturated and aromatic hydrocarbons is the key step in gold-catalyzed organic transformations",¹⁷ and gold(III) has a long history of interacting with arenes. For example, it has been known for over 80 years that anhydrous AuCl_3 reacts readily with aromatic hydrocarbons leading C-H auration of the arene.¹⁸ However, to date, all attempts to experimentally prepare stable molecules demonstrating Au-arene interactions have been unsuccessful.¹⁷ Nonetheless, such η^2 -arene gold(III) π -complexes species have been explored computationally,¹⁹ and are implicated as precursors to C-H auration. In our previous studies,^{9h} this *intermolecular* π -complexation event was deduced to be turnover-rate limiting, and the relative rates of arylation a series of arenes shown to correlate with known stabilities of reference $\text{Ag}\pi$ -arene complexes, and HF/BF_3 Wheland-intermediates.^{9h} However, there was no indication from any of the data obtained, whether steps prior to the irreversible C-H auration, are reversible or not.

The reversibility of the arene π -complexation can be tested using the intramolecular cyclization. Thus although no KIE is exhibited intermolecularly (**4b** versus d_5 -**4b**), an intramolecular competition reaction employing d_1 -**4b** was found to elicit a significant KIE ($k_{\text{H}}/k_{\text{D}} = 2.5$, equation 2) on the product distribution. In order for the primary KIE arising from C-H cleavage to impact on the product distribution (**5b** versus d_1 -**5b**), the isotopomeric precursor η^2 -complexes (**8** and **9**, Scheme 5) must be able to equilibrate prior to irreversible, i.e. product-determining, C-H / C-D cleavage. Equilibration could occur within discrete Au-arene complexes (pathway A) or by reversible η^2 -complexation (pathway B). The same primary KIE ($k_{\text{H}}/k_{\text{D}} = 2.5$) was obtained with bis-arene d_5 -**10** (Scheme 4, equation 3) confirming that Au-arene π -complexation is reversible, with C-H / C-D cleavage being product-determining, but not turnover-rate limiting (no KIE, Scheme 4 equation 1).



Scheme 5. η^2 -arene π -complexes and C-H auration mechanisms.

The KIEs outlined in equations 1-3 are consistent with both a concerted metalation-deprotonation (CMD) pathway,²⁰ and an aromatic electrophilic substitution ($\text{S}_{\text{E}}\text{Ar}$) pathway,^{9h,18,21} both stemming from a presumed precursor η^2 -complex, Scheme 5. When the methylene bridge in d_1 -**4b** is replaced with an O-atom linker, d_1 -**4v**, the primary KIE is nearly eliminated (Scheme 4, equation 4), suggesting that the aryl-ether is able to sufficiently stabilize the π -complex (CMD), or the Wheland intermediate ($\text{S}_{\text{E}}\text{Ar}$) such that one of these two steps, rather than the C-H / C-D cleavage, becomes product-determining.

C-H Auration via $\text{S}_{\text{E}}\text{Ar}$ versus CMD Having established that, for **4b** and **10a**, C-H cleavage is irreversible and thus product-determining (Scheme 4, equations 1-3), we studied intramolecular competition (**10b-f**) between electronically biased pairs of arenes, equation 5. This allows distinction of reaction *via* a monoaryl gold Wheland intermediate ($\text{S}_{\text{E}}\text{Ar}$) from C-H deprotonation of a π -complex (CMD), both leading to the same diaryl gold intermediate. A large negative ρ value was obtained ($\rho = -3.7$; see SI). In a concerted metalation-deprotonation (CMD) the acidity of the proton is of importance^{20b} and the net (negative) inductive effects of substituents dominate, leading to a complex but overall *positive* ρ -correlation, which is not observed. In contrast, stabilizing (positive) inductive and resonance effects of substituents are expected to be of importance in an $\text{S}_{\text{E}}\text{Ar}$ process, leading to a *negative* ρ/ρ^+ -correlation.²²

Turnover-limiting Reductive Elimination Reaction rates (Ms^{-1}) were determined under standard conditions (0.1 M substrate, 2 mol% thtAuBr_3) for a series of 18 substrates in which the arene (**4a-m**) or arylsilane (*iso*-**4i-m**) or bears a substituent that is *meta* or *para* to the site of coupling in **5a-m**, Figure 2. In addition to singly substituted substrates, bis-silyl **12** and doubly-substituted **4t** / **13** were also tested. The kinetics were analyzed by way of a linear free-energy relationship (LFER) using the standard Hammett σ -function, affording a reaction constant (ρ) of -2.0 .

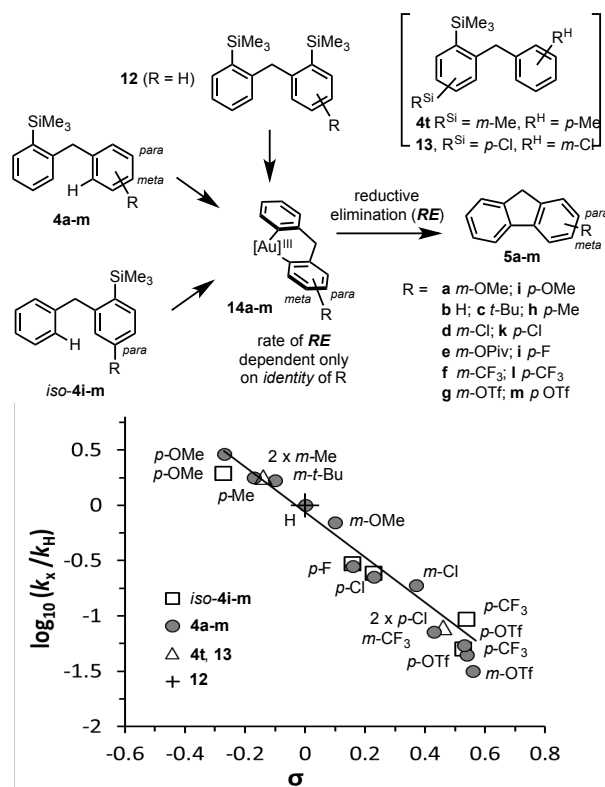


Figure 2. LFER analysis of rates of catalytic turnover during cyclization of **4a-m**; **4t**; *iso*-**4i-m**, **12**, and **13**; $\log_{10}(k_{\text{x}}/k_{\text{H}}) = -2.0 \sigma - 0.06$;²³ σ -values are additive for **4t**/**13**. Conditions: substrate (0.05 mmol), thtAuBr_3 (2 mol%), 2-bromothiophene (0.5 mmol),²⁴ $\text{PhI}(\text{OAc})_2$ (0.055 mmol), CSA (0.065 mmol), $\text{CDCl}_3/\text{CD}_3\text{OD}$ (50:1, 0.1 M).

The correlation indicates that the impact of a substituent on the rate of catalytic turnover is independent of its provenance; i.e. whether it was initially on the arene (**4a-m**), the arylsilane

(*iso*-**4i-m**), or on both (**4t**, **13**). This requires that the substrates converge on a common intermediate, at, or prior to, the turnover-rate limiting step. This condition can be satisfied at any point *after* C-H cleavage to generate a diaryl-gold intermediate. Further evidence for convergence at a common intermediate arises from the identical rates of turnover of *bis*-TMS **12** and *mono*-TMS **4b** (R = H), both of which generate **5b** *via* reductive elimination from the same intermediate (**14b**, Figure 2, R = H). Reaction of *bis*-TMS **12** thus involves a *second* C-Si cleavage, rather than C-H cleavage, at the stage of the mono-aryl-gold intermediate. The selective intramolecular C-Si versus C-H auration is again consistent with an S_EAr process, with TMS-stabilization of the β -cation in the Wheland intermediate being favored.^{9b}

The pseudo zero-order kinetics observed for of *bis*-TMS **12** and *mono*-TMS **4b** limit the possibilities for a unimolecular turnover-rate limiting step to reductive elimination from a diaryl-gold intermediate (**14b**), or ligand dissociation prior to this.²⁵ Reductive elimination is rarely the turnover limiting step in $C(sp^2)-C(sp^2)$ cross-coupling.²⁶ In most cases, oxidative addition or transmetalation is rate-limiting. Indeed, as a consequence of this, there has been a reliance on *stoichiometric* studies to indirectly investigate reductive-elimination in catalytic systems.^{9g,9i,9j,27} Details relating to the kinetics and structures involved in reductive elimination of a biaryl moiety from diaryl-gold species are very sparse. There are very few examples of isolated diaryl-gold complexes in which the aryls groups are simple, *i.e.* non-chelating.^{9h,28} Nevado was able to isolate and characterize (X-ray)^{9jk} the neutral di-aryl complex $[Ar_2Au(PPh_3)Cl]$ where Ar = C_6F_5 , and found that forcing conditions were required to trigger reductive elimination of perfluorobiphenyl (150 °C, 20 h).^{9j}

Pioneering studies by Kochi on trialkyl- and dialkyl-gold phosphine complexes $R_3Au(PPh_3)$ and $R_2Au(PPh_3)X$ (where R = Me, Et; X = Cl, TFA, NO_3 , OTf), revealed that that dissociation of PPh_3 , leading to high-energy T-shaped species R_3Au and R_2AuX , precedes reductive elimination of R-R.²⁹ In most cases, the overall rate of reductive elimination was slow ($k_{obs} = 10^{-6}$ to 10^{-7} s⁻¹ at 45–80 °C) and the liberated PPh_3 progressively inhibited reaction by disfavoring the dissociative pre-equilibrium. The exception to this trend was $Me_2Au(PPh_3)OTf$, which reductively eliminated very rapidly ($k_{obs} > 10$ s⁻¹ at 25 °C). The possibility of an additional pathway for reductive elimination involving triflate dissociation to generate cationic $[Me_2Au(PPh_3)]^+$ could not be discounted.^{29b}

More recently, Toste has confirmed that, for specific cases, phosphine dissociation is not necessary for reductive elimination to occur.^{9g} The neutral complex $[Ar_2Au(PPh_3)Cl]$, where Ar = $p-C_6H_4F$, was generated *in situ*, and found to more efficiently undergo reductive elimination ($k_{obs} = 10^{-4}$ s⁻¹ at -52 °C) than the analogous perfluoroaryl complex studied by Nevado.^{9j} In contrast to the inhibiting effects of added phosphine noted by Kochi, addition of PPh_3 , to generate the cationic bis(phosphine) complex $[Ar_2Au(PPh_3)_2]^+$, resulted in substantial rate enhancement ($k_{obs} = 0.2$ s⁻¹ at -52 °C). This process is “among the fastest observed C-C bond-forming reductive couplings at any transition metal centre.”^{9g} The high reaction velocity is ascribed to a combination of Au(III)-destabilization by the formal cationic charge at the gold, and the driving force provided by steric de-compression of the bulky triphenyl phosphine ligands as the

biaryl elimination proceeds.^{9g} Thus overall, a very wide range of rates have been determined for reductive R-R elimination from gold (III) species, with a number of contributing factors, including coordination number, formal charge, steric demand of ligands, and the electron demand by the Ar / alkyl groups undergoing elimination. The turnover-rates of the intramolecular Au-catalyzed process considered herein (up to 1 s⁻¹, 27 °C, **4n**, Table 2) are significantly slower than that of the stoichiometric reductive elimination from cationic $[Ar_2Au(PPh_3)_2]^+$, but not dissimilar to that for the neutral complex $[Ar_2Au(PPh_3)Cl]$.^{9g,30}

Based on the kinetic studies of Kochi,²⁹ the reductive elimination is expected to occur after ligand-dissociation from a neutral four-coordinate precursor (**15b**, Figure 3, L = unspecified neutral ligand, *e.g.* arene, solvent). ¹H NMR spectroscopic analysis of the Au-catalyzed intramolecular arylation of **4b** in $CDCl_3$ / CD_3OD at 27 °C revealed a transient low-intensity methylene signal, not attributable to traces of Ph_2CH_2 or catalyst-activation co-products (see SI). The signal was tentatively assigned to the -CH₂- tether in **15b**. Integration against an internal standard allowed analysis of the temporal concentration of **15b**, at three different initial *thtAuBr₃* precatalyst loadings (1.0, 1.5 and 2.0 mol%), Figure 3.

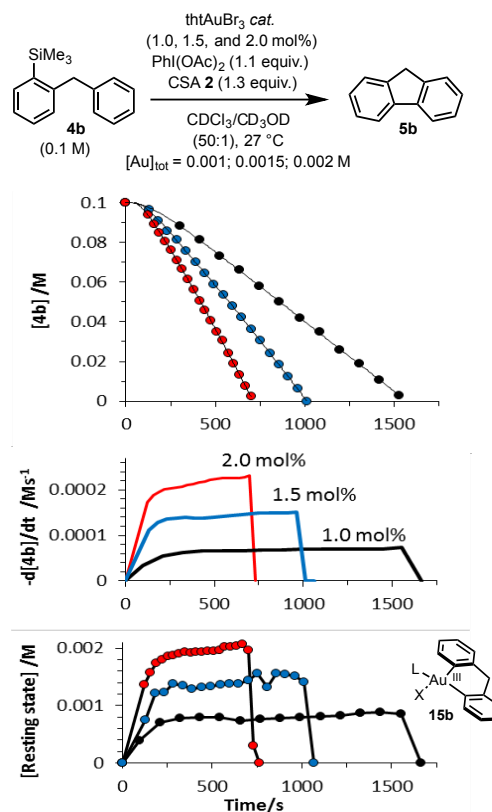


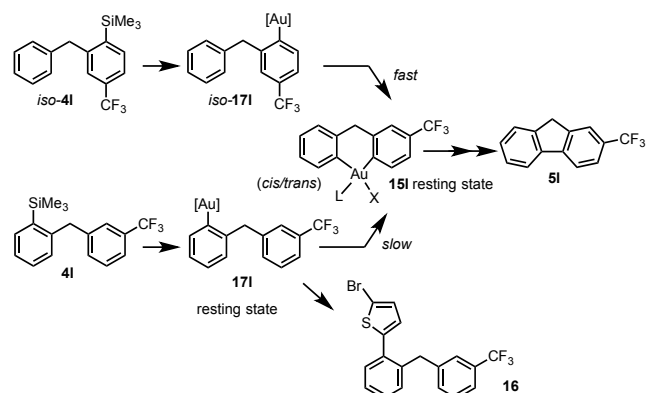
Figure 3 Top: Pseudo-zero order kinetics (after induction period, approx. 300 sec.)^{9h} for Au-catalyzed intramolecular arylation of **4b** using 1.0, 1.5 and 2.0 mol % Au. Middle: temporal turnover-rate of **4b** /M s⁻¹.³¹ Bottom: temporal concentration of catalyst resting state, tentatively assigned as **15b**; L = unspecified neutral ligand, *e.g.* arene, solvent; X = unspecified anionic ligand.

Analysis of the steady-state maximum concentration of the transient species (resting state, **15b**; Figure 3, bottom) confirmed that it accounts for >90% of $[Au]_{tot}$. Moreover, the con-

centration of **15b** can be correlated with the temporal changes in turnover-rate ($-d[4b]/dt$, $M s^{-1}$), Figure 3, middle. Thus the during the induction period (approx 300 sec.) the concentration of **15b** rises from zero to reach the steady-state, which is maintained throughout the pseudo zero-order phase of turnover. On complete consumption of substrate **4b**, the concentration of **15b** rapidly decays to zero.

Effect of aryl electron-demand and Au-Ar conformational mobility on Reductive-Elimination rates The acceleration of reductive-elimination by electron-donating substituents ($\rho = -2.0$; Figure 2) is partially consistent with literature precedent for other $Ar_2[M]$ complexes ($M = Pt, Pd$), where electron-withdrawing substituents are found to strengthen the ground-state metal-carbon bonds.^{27b,32} Hartwig showed, from LFER analyses, that reductive elimination from $Ar_2[Pt]$ “is faster from complexes with a larger difference between the electron-donating properties of the two aryl groups.”^{27b,32} In other words, the electronic effects of substituent on reductive elimination rates are not simply additive. In contrast, a recent computational study on reductive elimination from $cis-[AuPPh_3(Ar^1)(Ar^2)]$ complexes suggests that the electronic effects of aryl substitution are additive.³³ This is now experimentally confirmed: disubstituted compounds **4t** and **13** generate di-aryl-gold intermediates that reductively eliminate at rates predicted by the sum of their σ -values (Figure 2).

Whilst most cyclizations gave pseudo-zero order profiles (e.g. **4b**, Figure 3), the two slowest-reacting examples (*p*-CF₃ **4l**, *m*-OTF **4g**, Figure 2), where the arene ring is substituted by electron-withdrawing groups, showed distinct curvature.³⁴ This is indicative of turnover-rate limiting arene π -complexation from a mono-aryl-gold(III) resting state (**17**, Scheme 7),^{9h} which was tested by intermolecular interception of **17l** with a π -rich arene, resulting in co-generation of biaryl **16**.³⁵



Scheme 7. Dependency of resting state identity (**15** versus **17**) on the π -complexing ability of the arene. Conditions: **4l** / *iso-4l* (0.05 mmol), $thtAuBr_3$ (2 mol%), $PhI(OAc)_2$ (0.055 mmol), CSA (0.065 mmol), $CDCl_3/CD_3OD$ (50:1, 0.1 M), 2-bromothiophene (0.5 mmol), 27 °C. See SI for an analysis of **5l** / **16** partitioning as a function of conversion.

Calculations on reductive elimination from unconstrained²⁸ $[(Ar^1)(Ar^2)Au(PPh_3)Cl]$ and $[(Ar^1)(Ar^2)Au(PPh_3)]^+$ complexes show that the lowest energy transition state for involves Au-Ar conformations in which the two aryl rings are oriented face-to-face.³³ If this arrangement is made less energetically accessible, e.g. by strain, tethering or chelation,²⁸ then rates of reductive

elimination will be reduced. Longer, non-rigid, tethers are expected to allow greater Au-Ar conformational mobility and thus a lower energetic barrier to the attainment of the requisite face-to-face orientation of the two aryl rings. However, longer tethers will also reduce the effective molarity of the arene in the precursor C-H auration. The kinetics of cyclization of **4b** ($-CH_2-$ tether) are distinct from those of **4x** ($-CH_2CH_2-$ tether). In the latter case, increase of the tether length by one methylene unit results in a curved kinetic profile³⁴ (Figure 4), indicative of a mono-aryl-gold(III) resting state.^{9h}

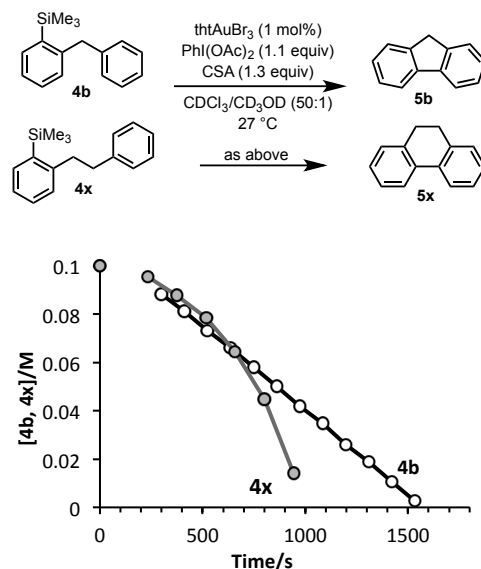


Figure 4. Turnover to generate 5- versus 6- membered rings. Initial concentration of **4b** and **4x** 0.1 M. As reaction proceeds, the turnover rate of **4x** accelerates,³⁴ becoming faster than that of **4b**.

A key observation is that as the reaction evolves, the rate of turnover of **4x** becomes faster than that of **4b**, for which reductive-elimination is turnover-rate limiting. In other words, the intrinsic rate of reductive-elimination from the longer $-CH_2CH_2-$ tethered intermediate **14x**, must be faster than that from the more constrained, $-CH_2-$ tethered, intermediate **14b** (Figure 5).³⁶

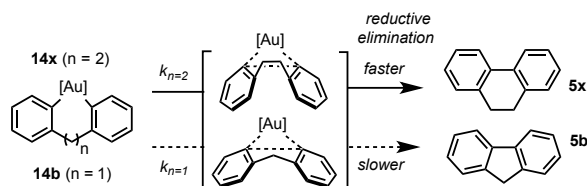
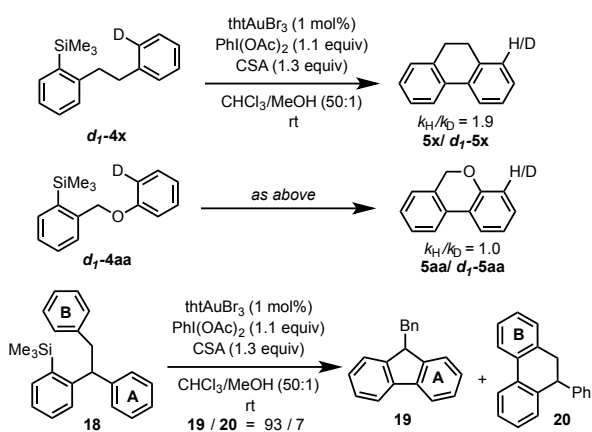


Figure 5. Effect of tether length (n) and flexibility on Ar-Au-Ar conformers from which developing Ar-Ar π -facial interaction^{28,33} can facilitate reductive elimination.

A normal primary KIE of 1.9 was obtained on intramolecular competition using $-CH_2CH_2-$ tethered d_1 -**4x**, indicative that Wheland intermediate generation is partially reversible (Scheme 6). Once again, stabilization of the Wheland intermediate by replacing the a CH_2 linker by oxygen (d_1 -**4aa**) eliminates the KIE. The impact of tether length ($n = 1, 2$) was further explored by intramolecular competition using **18** (Scheme 7). The 5-

membered ring cyclization outcompetes the 6-membered ring forming process by a factor of 13, consistent with *selectivity-determining*, i.e. irreversible, C-H cleavage after Wheland intermediate generation by ring A.³⁷



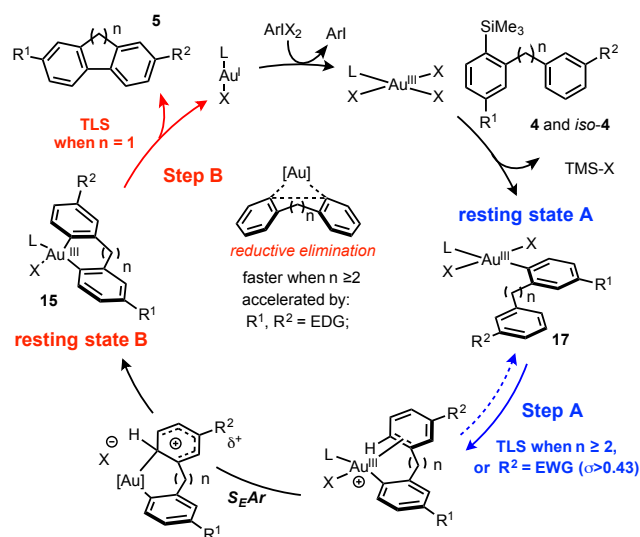
Scheme 7. KIEs for 6-membered ring cyclization of **4x** and **4aa**, and intramolecular competition (A versus B) to generate 5-membered (**19**) versus 6-membered (**20**) rings.

Conclusions

In 2012 we introduced a gold-catalyzed intermolecular direct arylation reaction that uses arylsilanes to catalytically-generate highly electrophilic Ar-Au intermediates capable of arylating arenes at ambient temperature.⁵ The reaction has proven to be a high-yielding, mild and efficient process for the coupling of a wide variety of arylsilanes with electron-rich arenes and heteroarenes.⁵⁻⁸ Herein we have studied the intramolecular version of the arylation, both as a preparative process, and as a vehicle for mechanistic study. Using a standard set of conditions, 44-examples of annelated-biaryls, with ring sizes ranging from 5- to 9-membered, including heteroatoms and a diverse range of arene substituents, have been prepared under mild conditions at ambient temperature (Table 2, Schemes 4, 6).³⁸ Whilst the majority of the reactions proceed with minimal side-product generation, some highly electron-rich substrates are susceptible to a competing direct reaction with the ArIX₂ oxidant (HCIB, **2**) to generate diaryliodonium salts. In such cases, PIFA (**3**) can be used as a milder reagent to attenuate this undesired oxidation. This effect is unique to the intramolecular process, and facilitates the clean arylation of even highly electron-rich arenes, such as the trimethoxy-benzene moiety of the allocolchinoid skeleton **7**,¹⁵ Scheme 3.

Rendering the arylation process intramolecular induces a number of changes that facilitate mechanistic investigation. Firstly, unlike the intermolecular system, the vast majority of the intramolecular substrates undergo turnover with simple and reproducible kinetics, without complications from side reactions such as arene oxidation or arylsilane homocoupling. Secondly, only electron rich arenes can be arylated intermolecularly, limiting the range of arene substituents that can be explored in linear free-energy relationships. In contrast, the intramolecular system tolerates a wide range of arene substituents, both electron donating and electron withdrawing, and the kinetics have been determined for substituents with σ -values ranging from -0.3 to +0.6. Thirdly, relative to all of the other Au(III)-mediated

steps³⁹ in the intermolecular catalytic cycle, reductive elimination from diaryl-gold(III) is fast. Consequently, it has not previously been possible to acquire kinetic data for this key C-C bonding forming process. Application of the intramolecular system has been pivotal in this regard. It allows two effects to be used in concert: a) tethering the arene to the arylsilane induces high effective molarity and raises the velocity of the C-H auration step, whilst b) close-tethering of the aryls decreases the velocity of the reductive elimination. In certain cases these two effects (a,b) have been sufficient to move the catalyst resting state to the diaryl-gold(III) intermediate, allowing a detailed analysis of the influence of substituents on the rate of reductive elimination.



Scheme 8. Mechanism of Au-catalyzed intramolecular arylation (**4** \rightarrow **5**) with turnover-rate limiting step (TLS) proceeding from a mono-aryl- (**17**) or di-aryl- (**15**) gold resting state, depending on tether-length (n), and electronic influence of arene substituent (R^2). L = unspecified ligand: arene, solvent. X = CSA, Br. For reductive elimination L = vacant site (**14**).

Using the unique features of the intramolecular variant of the arylation process, we have been able to elucidate the following:

- ²H-kinetic isotope effects (KIEs, Schemes 4 and 7) support our previous conclusion^{5,9h} that the C-H auration involves aromatic electrophilic substitution (S_EAr)²¹ via a Wheland intermediate, rather than a concerted metalation-deprotonation (CMD) pathway.²⁰
- When the aryl-arene tether is $-CH_2CH_2-$, despite the high effective molarity of the arene, the C-H auration, beginning with step A (Scheme 8), is the turnover-rate limiting step (TLS).^{9h}
- Reduction of the tether length from $-CH_2CH_2-$ to $-CH_2-$ results in a migration of the turnover-rate limiting step (TLS) from step A to step B, Scheme 8; but only when the arene is sufficiently π -complexing ($\sigma \leq 0.43$).
- Reductive-elimination from a diaryl-gold(III) intermediate generates the biaryl product **5** (step B) and is accelerated by electron-donating substituents (R^1, R^2) on the aryl rings. The effect is independent of whether the substituent was originally on the arylsilane or the arene ring. The acceleration correlates

with standard σ -values for R^1, R^2 , and if both rings are substituted, the effect is additive ($\sigma_{\text{net}} = \sigma\text{-}R^1 + \sigma\text{-}R^2$).

v) There is a requirement for a face-to-face arrangement of the two aryl rings during reductive elimination (step B). The shorter $-\text{CH}_2-$ tether results in a slower rate of reductive elimination compared to the longer $-\text{CH}_2\text{CH}_2-$ unit, as the latter allows greater conformational freedom for the system to attain the required arrangement of the two aryl rings.

In summary, the investigation of catalytic reaction mechanism plays an important role in the discovery and development of new synthetic methodology. It can lead to useful generalizations and design principles in the optimization and application of catalysis. However, mechanistic studies are often limited to a small collection of well-behaved substrates, or constrained to a narrow range of accessible reaction conditions. In such cases, mechanistic insight must be extrapolated with caution, even for what may appear to be a closely related system: the assumption that the same parameters and constraints apply, may not be valid. The results presented herein demonstrate exactly such a situation. Even small changes in the substrate structure lead to different mechanistic behaviors. Thus by changing a single aryl substituent from being above or below $\sigma = 0.43$, or by varying the tether length by one methylene unit, the catalyst resting state can switch from one side of the cycle to the other (A versus B, Scheme 8). The last step of the cycle, the Au(I)/Au(III) redox by ArIX_2 reagents (e.g. 2 and 3), remains one for which there is very little mechanistic detail. Rapid redox is essential for the success of the reaction;³⁹ this process is under active investigation.

ASSOCIATED CONTENT

Additional discussion, experimental procedures, kinetic data, characterization data, and NMR spectra. This material is available free of charge via the internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

guy.lloyd-jones@ed.ac.uk

Notes The authors declare no competing financial interest.

Funding Sources The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° [340163].

REFERENCES

- (1) a) *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Bräse, S., Oestreich, M., Eds.; Wiley-VCH Verlag GmbH & Co: Weinheim, Germany, 2014. b) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085; c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.
- (2) Hussain, I.; Singh, T. *Adv. Synth. Catal.* **2014**, *356*, 1661–1696
- (3) For reviews on direct arylation, see: a) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138–12204; b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345; d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169; e) *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; f) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464.
- (4) For reviews on gold catalysis, see: a) Pfalterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331–1367; b) Zi, W.; Toste, F. D. *Chem. Soc. Rev.* **2016**, *45*, 4567–4589; c) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* **2016**, *45*, 4448–4458; d) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028–9072; e) Deharo, T.; Nevado, C. *Synthesis* **2011**, 2530–2539; f) Wegner, H. A.; Auzias, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8236–8247; g) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211; h) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, *4*, 333–346; i) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936.
- (5) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012**, *337*, 1644–1648.
- (6) Hata, K.; Ito, H.; Segawa, Y.; Itami, K. *Beilstein J. Org. Chem.* **2015**, *11*, 2737–2746.
- (7) Hua, Y.; Asgari, P.; Avullala, T.; Jeon, J. J. *Am. Chem. Soc.* **2016**, *138*, 7982–7991.
- (8) Cresswell, A. J.; Lloyd-Jones, G. C. *Chem. Eur. J.* **2016**, *22*, 12641–12645.
- (9) For reviews on reactivity and isolation of gold complexes, see: a) Joost, M.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 15022–15045; b) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241. For selected recent advances in the field, see: c) Kawai, H.; Wolf, W. J.; DiPasquale, A. G.; Winston, M. S.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 587–593; d) Joost, M.; Estévez, L.; Miqueu, K.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 5236–5240; e) Winston, M. S.; Wolf, W. J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 7921–7928; f) Wu, C.-Y.; Horibe, T.; Jacobsen, C. B.; Toste, F. D. *Nature* **2015**, *517*, 449–454; g) Wolf, W. J.; Winston, M. S.; Toste, F. D. *Nat. Chem.* **2014**, *6*, 159–164; h) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *J. Am. Chem. Soc.* **2014**, *136*, 254–264; i) Wu, Q.; Du, C.; Huang, Y.; Liu, X.; Long, Z.; Song, F.; You, J. *Chem. Sci.* **2014**, *6*, 288–293; j) Hofer, M.; Gomez-Bengoia, E.; Nevado, C. *Organometallics* **2014**, *33*, 1328–1332; k) Hofer, M.; Nevado, C. *Eur. J. Inorg. Chem.* **2012**, 1338–1341.
- (10) For pioneering studies into intramolecular direct arylation, see: a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015–6020; b) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590. c) Campeau, L. C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187.
- (11) For select examples of 7-, 8- and 9- membered ring synthesis via direct arylation, see: a) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2011**, *133*, 1209–1211; b) Majumdar, K. C.; Ray, K.; Ganai, S. *Tetrahedron Lett.* **2010**, *51*, 1736–1738; c) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. J. *Org. Chem.* **2008**, *73*, 1888–1897; d) Beccalli, E. M.; Brogini, G.; Martinelli, M.; Paladino, G.; Rossi, E. *Synthesis* **2006**, 2404–2412; e) Bressy, C.; Alberico, D.; Lautens, M. J. *Am. Chem. Soc.* **2005**, *127*, 13148; f) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849–2852; g) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207–5209; h) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317.
- (12) Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M. *J. Org. Chem.* **1990**, *55*, 315–318.
- (13) For a review on synthesis and application of diaryliodonium salts, see: Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070.
- (14) Increased yields are only obtained with the most electron-rich substrates. PIFA (3) does not lead to productive catalysis in intermolecular examples; presumably because it does not release a strong-enough acid (such as CSA) to catalyze the methanol-dissociation for π -complexation / C-H auration.^{9h}
- (15) For examples of syntheses of this scaffold, see: a) Djurdjevic, S.; Yang, F.; Green, J. R. *J. Org. Chem.* **2010**, *75*, 8241–8251; b)

- Besong, G.; Jarowicki, K.; Kocienski, P. J.; Sliwinski, E.; Boyle, F. T. *Org. Biomol. Chem.* **2006**, *4*, 2193–2207; c) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826–5831.
- (16) For a recent review on transition-metal-catalyzed synthesis of fluorenes, see: Zhou, A.-H.; Pan, F.; Zhu, C.; Ye, L.-W. *Chem. Eur. J.* **2015**, *21*, 10278–10288.
- (17) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, *29*, 2–23.
- (18) Kharasch, M. S.; Isbell, H. S. *J. Am. Chem. Soc.* **1931**, *53*, 3053–3059.
- (19) Ghosh, M. K.; Tilset, M.; Venugopal, A.; Heyn, R.; Swang, O. J. *Phys. Chem. A* **2010**, *114*, 8135–8141.
- (20) For mechanistic studies on the CMD mechanism with palladium, see: a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658–668; b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. For a perspective on CMD in general see: c) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126; For a perspective on CMD with Pd d) Livendahl, M.; Echavarren, A. M. *Isr. J. Chem.* **2010**, *50*, 630–651.
- (21) For stoichiometric studies on the S_EAr / CMD mechanisms for gold, see: a) Kharasch, M. S.; Beck, T. M. *J. Am. Chem. Soc.* **1934**, *56*, 2057–2060; b) Liddle, K. S.; Parkin, C. J. *Chem. Soc., Chem. Commun.* **1972**, *26*; c) de Graaf, P. W. J.; Boersma, J.; van der Kerk, G. J. M. *J. Organomet. Chem.* **1976**, *105*, 399–406; d) Fuchita, Y.; Utsunomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans.* **2001**, 2330–2334; e) Rosca, D.-A.; Smith, D. A.; Bochmann, M. *Chem. Commun.* **2012**, *48*, 7247–7249; f) Hofer, M.; Nevado, C. *Tetrahedron* **2013**, *69*, 5751–5757; g) Cambeiro, X. C.; Boorman, T. C.; Lu, P.; Larrosa, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 1781–1784. Under catalytic conditions, see: h) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. *J. Am. Chem. Soc.* **2015**, *137*, 15636–15639. See also ref 9h.
- (22) A 'normal' p value would be expected for π -complexation, whereas a p^+ value would be expected for Wheland intermediate generation, see reference 9h. The KIEs obtained with **10a** indicate π -complexation is reversible for simple phenyl rings. However, the rate data do not give an ideal linear correlation, and the electronically biased rings in **10b-f** may shift the process away from Curtin-Hammett control such that the ratios begin to reflect the equilibrium population.
- (23) Standard Hammett σ -values were employed (Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195) except for the value for p -F where, in our experience, $\sigma_p = 0.15$ (Shulgin, A. T.; Baker, A. W. *Nature*, **1958**, *182*, 1299) is better parameterized for reactions in non-aqueous media, as compared to the standard value of $\sigma_p = 0.06$ which was determined in water.
- (24) Kinetic profiles obtained with electron deficient arylsilanes were partially non-linear, this was resolved by addition of 2-bromothiophene. The detailed kinetics of this phenomenon are currently under investigation. Arenes **4l** (p -CF₃) and **4g** (m -OTf) also gave curved kinetic profiles (i.e. imperfect pseudo zero order kinetics) that were not linearized by addition 2-bromothiophene. The rate averages were employed for the correlation, and are slightly lower than predicted by $\log_{10}(k_x/k_H) = -2.0\rho - 0.06$. See Figure 6 and associated text for more detailed discussion, and SI for rate limits.
- (25) The large ΔS^\ddagger value (Fig 1) may be an apparent activation parameter, arising from combination of a pre-equilibrium dissociation with irreversible reductive elimination from a three-coordinate intermediate.
- (26) a) Jin, L.; Zhang, H.; Li, P.; Sowa, J. R.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 9892–9893; b) Amatore, C.; Jutand, A. *Organometallics* **1988**, *7*, 2203–2214.
- (27) a) Osakada, K.; Onodera, H.; Nishihara, Y. *Organometallics* **2005**, *24*, 190–192; b) Shekhar, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 13016–13027; c) Merwin, R. K.; Schnabel, R. C.; Koola, J. D.; Roddick, D. M. *Organometallics* **1992**, *11*, 2972–2978; d) Braterman, P. S.; Cross, R. J.; Young, G. B. *J. Chem. Soc. Dalt. Trans.* **1977**, 1892–1897.
- (28) Reductive elimination from chelated Ph-Au(X)-(Ar-N-donor) complexes requires addition of PPh₃ to displace the N-donor: Vicente, J.; Dolores Bermudez, M.; Escribano, J. *Organometallics* **1991**, *10*, 3380–3384; see also reference 9i
- (29) a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 7255–7265; b) Komiya, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 7599–7607; c) Tamaki, A.; Magennis, S. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 6140–6148.
- (30) Use of the reported activation parameters (ref 9g) for Ar₂Au(PPh₃)Cl, indicates that the rate of reductive elimination of this system at 27 °C is about 5 s⁻¹.
- (31) Turnover rates were estimated by differentiation of high-order polynomial fits to the temporal concentration plots.
- (32) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936–1947.
- (33) a) Nijamudheen, A.; Karmakar, S.; Datta, A. *Chem. Eur. J.* **2014**, *20*, 14650–14658.
- (34) Rates for these substrates are dependent on the CSA concentration, see SI, which rises as oxidant (**2**) is consumed. The curvature does not arise from a longer induction period; pre-catalyst activation is complete in around 300 seconds^{9h} (based on analysis of Ar-Br co-products, see SI) this being less than 2% of the time taken for complete turnover of the substrate.
- (35) Control experiments confirmed that the pseudo-zero order rate profile for cyclization of *iso*-**4l** is independent of CSA concentration, consistent with turnover of *iso*-**4l** via reductive elimination from the normal diaryl gold (**15l**) resting state. For systems bearing a -CH₂- tether, the transition from di- to mono-aryl-gold resting state is only observed for examples **4l** and **4g**, where the arene ring bears strongly electron-withdrawing groups ($\sigma_{\text{net}} \geq 0.43$). Bromothiophene-trapped products were not obtained with any substrates where $\sigma_{\text{net}} < 0.43$.
- (36) At this stage we cannot assess how much faster the reductive elimination to the 6-membered ring is, as the change in kinetic profile also suggests a change in the TLS; thus turnover-rate may be limited by π -complexation or reductive elimination, or both, at different stages in the reaction evolution.
- (37) This selectivity may arise from the differential developing strain in 6-membered versus 7-membered aurocycles generated from rings **A** / **B** respectively.
- (38) This applies to all but **4ai** (Table 2, entry 18) which required heating to 50 °C.
- (39) If the Au(I)X / Au(III)X₃ redox it is not sufficiently rapid (due to low oxidant concentration or kinetically-ineffective oxidant species) the Au(I) disproportionates, resulting in rapid catalyst deactivation.

Graphic entry for the Table of Contents (TOC).

